REMARKS/ARGUMENTS

With this amendment, claims 1, 15-18, 20, 24-25, and 27-29 are pending. New claims 28-31 are added. Claims 2-14, 19, 21-23 and 26 are cancelled. Applicants thank the Examiner for acknowledging that the claimed methods are not taught in the art, at page 4 of the Office Action. For convenience, the Examiner's rejections are addressed in the order presented in the November 2, 2004 Office Action.

I. Status of the claims

Claim 1 is amended to recite transplanting a stem cell-rich population of cells from a human donor, wherein the stem cell-rich population of cells has a beneficial gene that is a polymorphism in a CCR5 gene. Support for this amendment is found throughout the specification, for example, at page 9, lines 14-25; page 12, lines 1-13; and page 5, lines 26-29. Claims 18, 20, 24, and 27 depend from claim 1 and are now amended to recite the stem cell-rich population of cells. These amendments are not limiting amendments and add no new matter.

New claims 28 and 29 are added and recite a method step that was formerly step a) of claim 1. New claims 30 and 31 are added and are directed to determining the HLA phenotype or genotype of a human patient and transplanting an HLA compatible stem cell rich population of cells into that patient. Support for these amendments is found throughout the specification, for example at page 11, lines 15-17 and page 13, lines 9-14. These amendments are not limiting amendments and add no new matter. Claims 3-9, 11-13, 19, 21-23 and 26 are cancelled.

II. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1 and 15-27 are rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not provide sufficient guidance for those of skill to make and use the claimed invention. The Office Action also alleges that undue experimentation is required to practice the claimed invention. To the extent the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. *See, e.g., Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

As set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

The current Office Action alleges that an "undue" amount of experimentation is required by those of skill to practice the claimed invention. Office Action at page 3. The Office Action alleges that the specification does not provide sufficient guidance to isolate cells for use in the claimed methods. This is incorrect. The specification discloses sources for a stem cell-rich population of cells from a human donor: umbilical cord blood, placental blood, bone marrow, peripheral blood and adipose tissue. *See, e.g.*, specification at page 7, lines 23-25 and page 9, lines 21-25. The specification also teaches screening of cell populations for beneficial genes, such as polymorphisms in CCR5 and for the HLA genotype. *See, e.g.*, specification at pages 10-11. Applicants respectfully refer the Examiner to the incorporation by reference of

USSN 09/747,391, now U.S. Patent no. 6,670,124, at page 10, lines 21-29 and at page 11, lines 19-26. The '124 patent teaches high throughput methods for screening a cell samples from a donor to determine the genotype. Thus, identification of appropriate stem cell sources for transplantation was well within the abilities of a skilled artisan at the time of filing. The specification also discloses references that teach harvesting, enrichment and cryopreservation of the cells. Thus, isolation of the cells was know at the time of filing. Moreover, those of skill would recognize that all the cells taken from a single donor would have the same genotype, including any CCR5 polymorphisms. Thus, those of skill could assess the CCR5 genotype of a sample of the stem cell-rich population with only routine experimentation.

The Office Action also alleges that the use of the cells in treating a patient with HIV would have required undue experimentation to be practiced by one of skill. Applicants respectfully traverse. Bone marrow transplantation to replace the immune system of humans was well known at the time of filing. At the time of filing many symptoms of HIV infection, including progression to AIDS, were controlled by Highly Active Anti-Retroviral Therapy (HAART), a treatment protocol. Bone marrow transplantation of persons with AIDS related lymphoma, *i.e.*, patients with HIV infection, was also routinely done at the time of filing. Bone marrow transplantation of patients with HIV is described in Levine *et al.* Hematology 2001, page 463-478, which is submitted herein as Exhibit A. Thus, bone marrow transplantation to persons with HIV infection was practiced at the time of filing and did not require undue experimentation by those of skill. Moreover, given the knowledge of bone marrow transplantation in the art at the time of filing, the specification provides adequate guidance to practice such transplantation methods.

The specification also alleges that no animal models are disclosed in the specification. This is incorrect. First, the CCR5 mutations were identified through studies of humans who had repeatedly been exposed to the HIV virus, but were not infected. The mutation in the CCR5 gene was determined to reduce the ability of the HIV virus to enter CD4+ cells. Homozygous mutants did not become infected, while heterozygous mutants showed delayed progression of the disease, as compared to individuals with a homozygous wild type CCR5 gene.

In addition, the specification at page 7, line 30 through page 8, line 3 teaches a mouse model of the disease. Cells from a human donor are transplanted into an appropriate mouse and used to model the disease. The usefulness of this model is demonstrated in Picchio *et al. J. Virol.* 71:7124-7127 (1997), which is herein submitted as Exhibit B. Picchio *et al.* used mice that do not produce B or T cells, *e.g.*, severe combined immunodeficiency (SCID) mice. These mice can be transplanted with immune cells from human donors and were transplanted with cells from humans with the following CCR5 genetypes: homozygous mutant CCR5 Δ32/Δ32, heterozygous mutant CCR5 Δ32/+, or wild type CCR5 +/+. The mice were then infected with HIV virus. The homozygous mutant CCR5 mice were resistant to M tropic virus, and did not exhibit viral replication. The wild type CCR5 mice exhibited the fastest time to maximum viral replication values. The heterozygous CCR5 mutant had significantly delayed viral replication kinetics after infection with the M tropic virus. These results mimic the phenotypes of the original human CCR5 mutations. Thus, based on both the specification and the art at the time of filing, those of skill would be able to practice the claimed invention without undue experimentation.

The Office Action objects to the listing of beneficial genes CD4, CCR2, CCR2-641 in claims 11-14. However, these claims were withdrawn after a restriction requirement and are now cancelled. The Office Action also appears to reject claims that recite a beneficial gene, generally. Applicants believe that the response to the restriction requirement and amendment of claims with the previous response should overcome this rejection. Therefore, any arguments based on the listing of beneficial genes CD4, CCR2, CCR2-641 in claims 11-14, or on beneficial genes generally, should be withdrawn.

The Office Action also cites a reference by O'Brien and Dean as demonstrating that some CCR5mutations could backfire and encourage advancement to AIDS. The O'Brien and Dean article was written in 1997 and apparently the authors did not appreciate the difference between M tropic and T tropic HIV viruses.

The Office Action at page 5, appears to state that the specification does not teach how to screen for a stem cell from which all differentiated cells would have a certain

polymorphism. Applicants respectfully point out that it is a central tenant in biology that cells that divide mitotically, including stem cells, give rise to progeny that all carry essentially identical genomes, *i.e.*, phenotypes. If the Examiner is aware of any reference that disputes this, either for a genome as a whole or for a particular CCR5 polymorphism, the Examiner is respectfully invited to cite it. The Office Action also appears to express concern over the amount of a beneficial gene required for protective effect. The answer is found in the naturally occurring human "mutants." Homozygous CCR5 mutants did not become infected, while heterozygous CCR5 mutants showed delayed progression of the disease, as compared to individuals with a homozygous wild type CCR5 gene. Thus, therapeutic benefit can be had from reduction or elimination of functional CCR5 protein.

The Office Action asserts that expansion of the stem cells is not taught by the specification. In order to expedite prosecution, claim 19 is now cancelled.

The Office Action alleges that the specification does not provide guidance about the patient to be transplanted or the state of endogenous stem cells in the patient, or how such cells will be eliminated. Applicants respectfully assert that the information is found in the specification at page 12, lines 14-19, which discloses that the patient's endogenous stem cell population is eliminated or reduced before transplant using chemotherapy, radiation, or techniques disclosed in U.S. Patent No. 6,217,867. Such techniques are well known to those of skill and further description is not required. The Office Action also expresses concern that the endogenous stem cell population could still be present and thus, spread the infection to the transplanted cells. In response, Applicants assert that transplants, *e.g.*, bone marrow transplants, are routinely given to patients with hematopoetic cancers. These patients also run the risk of surviving cancer cells outgrowing a transplanted population, but the therapeutic benefit is deemed to outweigh the risk. As no cure has been found for AIDS, the therapeutic benefit of the claimed methods, *e.g.*, increased time to development of AIDS or elimination of the virus, would also be seen by those of skill to outweigh any risk of reinfection.

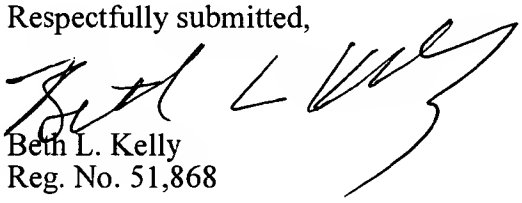
In view of the above arguments and remarks, withdrawal of the enablement rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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